REMARKS

Since there has been some discrepancy over pending claims, Applicants now reiterate the claim history. In the July 6, 2001 REPLY TO RESTRICTION REQUIREMENT, Applicants canceled all pending claims and added new claims 28-**54**. In the February 1, 2002 AMENDMENT, Applicants canceled claims 38, 39 and 41. In the September 23, 2002 AMENDMENT, Applicants added new claims 55 and 56. Hereinabove, Applicants have added new claims 57-58.

Accordingly, **claims 28-37, 40 and 42-58 are pending** and stand ready for further action on the merits. As the Examiner will note, claims 28-33, 50 and 51 were withdrawn from consideration based upon the June 6, 2001 Restriction Requirement and as indicated on the Office Action Summary (PTO-326 form) dated October 19, 2001.

In the above-amendment, claims 37 and 42 have been amended to be in independent form. Claims 40 and 56 have been amended to clearly set forth that the claim is drawn to an immunosuppressive *composition*. Support for new claims 57 and 58 can be found in claim 34. No new matter has been added by way of the above-amendment.

Interview

Applicants note with appreciation that the Examiner conducted a telephonic interview with Applicants' representative on March 10, 2003. During the interview, the Examiner acknowledged that he made an error in preparing the December 17, 2002 Office Action. The Examiner indicated that claims 42-44 have not been canceled and are pending. Applicants are now treating claims 42-44 as being included: (A) in the rejection under 35 U.S.C. §112, second paragraph (as described on pages 3-4 of the outstanding Office Action); and (B) in the rejections under 35 U.S.C. §102(b) and 103(a) over Coates et al. WO 93/22397.

Also, with regard to claims 55-56, the Examiner indicated that he made an error in preparing the December 17, 2002 Office Action. Specifically, the Examiner indicated that it was an error to indicate that claims 53-54 were never filed. The Examiner acknowledged that claims 53-54 are pending and are recited in the July 6, 2001 Reply to the Restriction Requirement. Accordingly, new claims 55 and 56, as appearing in the September 23, 2002 Amendment, will remain numbered as 55 and 56. Applicants herein treat claims 53 and 54 as appearing in the July 6, 2001 Reply to the Restriction Requirement, as being included: (A) in the rejection under 35 U.S.C. §112, second paragraph (as described on

pages 3-4 of the outstanding Office Action); and (B) in the rejections under 35 U.S.C. §102(b) and 103(a) over Coates et al. WO 93/22397. However, claims 55 and 56 are included in the rejection under 35 U.S.C. §112, second paragraph only and are not included in the prior art based rejections.

Also, during the interview, Applicants pointed out to the Examiner that there is a discrepancy in how claims 37 and 40 have been handled. Specifically, claim 40 is rejected under 35 U.S.C. §102(b) and §103(a) over Coates et al. while claim 37 is not included in these rejections. The Examiner indicated that claim 40 is included in these rejections, since the Examiner is treating claim 40 as being drawn to a compound and not a pharmaceutical composition as described in claim 37. In accordance with the Examiner's suggestion, Applicants have herein amended claim 40, at line 1, to more clearly recite that the immunosuppressor is an immunosuppressive composition.

Applicants now turn to the rejections set forth in the December 17, 2002 Office Action.

Issues Under 35 U.S.C. §112, second paragraph

Claims 34-37, 40, 42-49 and 52-56 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. Applicants respectfully traverse the rejection.

The Examiner maintains the rejections under 35 U.S.C. §112, second paragraph alleging that the term "prodrug" renders the claims indefinite. As the Examiner notes, the term "prodrug" refers to a compound which undergoes *in vivo* hydrolysis to the parent active drugs. The Examiner finds it confusing that the inventive claims include: (1) compounds of formula (I) which have substituents that may undergo *in vivo* hydrolysis; and (2) compounds of formula (I) which may be modified to include a substituent that gives the compound the ability to undergo *in vivo* hydrolysis.

On this matter, the Examiner states:

> First of all, the issue is not what a prodrug is but how would one distinguish a prodrug group from the groups already present in the molecule. A dual definition of the same group will create ambiguity thereby rendering the claims indefinite.

In response to the Examiner's arguments, Applicants first agree with the Examiner that the definition of a prodrug is a compound which undergoes *in vivo* hydrolysis. If the compound of Formula (I) has a substituent that enables the compound to undergo *in vivo* hydrolysis, then said compound is a prodrug. If the

compound of Formula (I) is modified to have a substituent that enables the compound to undergo *in vivo* hydrolysis, then said modified compound is a prodrug. This is simply not an ambiguous situation as asserted by the Examiner.

The key question is whether the skilled artisan would understand the scope of the present claims. Clearly, the skilled artisan would understand that overlap in the formulaic definition of the compounds with a prodrug of the compounds of formula (I) does not make the scope of the present claims unclear.

As MPEP 2173.02 instructs, Examiner's should allow claims which define patentable subject matter with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the Examiner might desire. Applicants respectfully requests that Examiner reconsiders his position and withdraws the rejection because all of the inventive claims describe the invention with a reasonable degree of particularity and distinctness.

Issues Under 35 U.S.C. §102 and §103

The following prior art rejections are pending:

(1) Claims 34-36, 40, 42-49, 53 and 54 are rejected under 35 U.S.C. §102(b) as being anticipated by Coates et al. WO 93/22397; and

(2) Claims 34-36, 40, 42-49, 53 and 54 are rejected under 35 U.S.C. §103(a) as being unpatentable over Coates et al.

Applicants respectfully traverse each of the rejections.

With regard to the rejection under §102(b), the Examiner directs Applicants' attention to example 3 on pages 65-67 and diagram 3 on page 79 of Coates et al. These compounds are taught to be useful for their liquid crystalline properties.

With regard to claim 40, Applicants respectfully submit that this claim is patentable, since claim 40 has been amended to more clearly recite a pharmaceutical composition.

With regard to independent claims 34, 45, 46 and 49, Applicants respectfully submit that these specific compounds cited by the Examiner in Coates et al. are excluded by *proviso*. As the Examiner will note, in each of the liquid crystalline compounds of Coates et al. cited by the Examiner, the central phenyl ring is substituted with one or two fluorine atoms while the others are hydrogen. However, in each of the independent

claims 34, 45, 46 and 49, the compounds of formula (I) are excluded when one or more of R^6, R^7, R^8 and R^9 (these are the substituents on the central phenyl ring) are halogen and the others are hydrogen.

According to MPEP §2131, a claim is anticipated only if each and every element is expressly or inherently described in the cited reference. Since the compounds of Coates et al. are excluded from the inventive claims, a *prima facie* case of anticipation can not be said to exist.

With regard to the rejection under 35 U.S.C. §103(a), Applicants respectfully submit that Coates et al. fail to fairly suggest modifying the central ring of the ter-phenyl core of example 3 on pages 65-67 and diagram 3 on page 79 of Coates et al. to either: i) remove the fluorine substitution of the central ring; or ii) substitute the central ring with additional substituents other than fluorine as in the compounds encompassed by the presently claimed invention.

As was mentioned in the February 1, 2002 Amendment, the prior art has recognized that small structural changes to the terphenyl rings could result in a compound that does not show liquid crystalline properties as required by Coates et al. Liquid crystals differ from either solids or liquids in that the

molecules are capable of diffusing in a manner like liquids, however, they will still retain a small degree of long range orientational and sometimes positional order thereby resulting in an anisotropic phase. These liquid crystal phases are thermodynamically stable for temperature ranges between the solid and isotropic liquid phases. There is a delicate balance between the intermolecular forces for the compounds to have a liquid crystal property.

As is clear from the disclosure of Coates et al., each of the central phenyl rings contains both fluorine and hydrogen bonded to the carbon at the 2, 3, 5 and 6 positions. Fluorine being a relatively small atom with high electronegativity, would affect both the structural arrangement of the terphenyl ring and the electron density on all three rings. Accordingly, the skilled artisan would **not** have a reasonable degree of certainty that the compounds, as presently claimed, would have liquid crystalline properties. As such, a *prima facie* case of obviousness can not be said to exist, and withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

Information Disclosure Statement

On March 1, 1999, Applicants timely filed an Information Disclosure Statement. Attached to the December 17, 2002 Office Action the Examiner returned a signed copy of the March 1, 1999 PTO-1449 form; however, the Examiner crossed out seven of the references indicating that the references were in the Japanese language and no translation was provided.

Applicants respectfully submit that the references, JP 5-25145, JP 65-07987 and JP 82-77247 were cited on the English language International Search Report submitted with the December 31, 1998 IDS. The English language International Search Report satisfies the requirement for a concise explanation.

Although there is no requirement, Applicants enclose herewith a copy of either English language abstracts or English equivalents of the crossed out references for the Examiner's convenience. Also, Applicants enclose a new PTO-1449 form listing the references.

US 4,495,202 is in the same patent family as JP 60-13730;
US 3,624,142 is in the same patent family as JP 43-19935;
US 4,728,670 is in the same patent family as JP 62-294650;
US 5,871,665 is in the same patent family as JP 65-07987;
US 5,750,051 is in the same patent family as JP 82-77247; and
US 5,968,980 is in the same patent family as WO 9618606.

Applicants respectfully request that the Examiner returns an initialed and signed copy of the enclosed PTO-1449 form in the next communication.

Conclusion

In view of the above amendments and comments, Applicants respectfully submit that the claims are in condition for allowance. A notice to such effect is earnestly solicited.

Applicants have attached hereto a marked up version of the claims to show the changes made for the Examiner's convenience.

If the Examiner has any questions concerning this application, he is requested to contact the Garth M. Dahlen, Ph.D. (#43,575) at the offices of Birch, Stewart, Kolasch & Birch, LLP at the number given below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Mard S. Weinery #32,181
P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

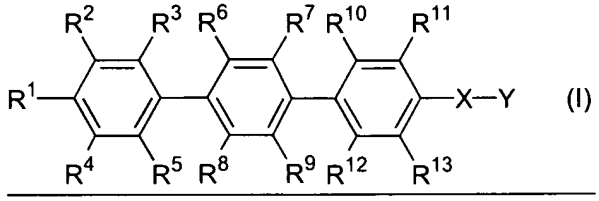
MSW/GMD/gh
0032-0248P
Attachments: Marked up Version Showing Changes Made
Copy of PTO-1449 form

Marked Up Version Showing Changes Made

IN THE CLAIMS:

The claims have been amended as follows:

37. (Twice Amended) A pharmaceutical composition comprising [the] a compound, pharmaceutically acceptable salt, hydrate or prodrug thereof [claimed in claim 34 or 35], and a pharmaceutically acceptable excipient, wherein the compound is of the formula (I):



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, hydroxy, halogen, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkenyloxy, optionally substituted lower alkylthio, optionally substituted lower alkoxycarbonyl, optionally substituted acyloxy, optionally substituted lower alkylsulfonyl, optionally substituted lower alkylsulfonyloxy, optionally substituted lower alkylsulfinyl, nitro, cyano, formyl, optionally substituted amino, optionally substituted carbamoyl, optionally substituted sulfamoyl or optionally substituted heterocyclyl,

X is -O-, $-CH_2-$, $-NR^{14}-$ wherein R^{14} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or acetyl, or -S(O)p- wherein p is an integer of 0 to 2,

Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl or optionally substituted heterocyclyl, and Y may optionally be substituted lower alkoxy when X is $-CH_2-$ and may optionally be substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyl or optionally substituted arylsulfonyl when X is -O- or $-NR^{14}-$,

R^1 and R^4, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^6 and R^7, R^8 and R^9, R^{10} and R^{11}, R^{12} and R^{13}, R^{11} and -X-Y, or R^{13} and -X-Y taken together may form a 5- or 6-membered ring which may contain one or more of O, S or NR^{15} wherein R^{15} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted arylsulfonyl and which may optionally be substituted,

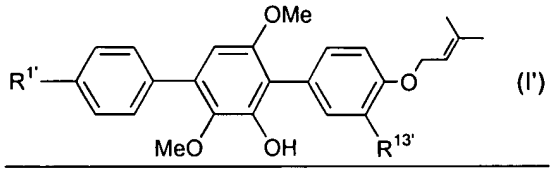
excluding compounds wherein one or more of R^6, R^7, R^8 and R^9 are halogen and the others are hydrogen, compounds wherein all of R^6,

R^7, R^8 and R^9 are halogen and compounds wherein all of R^2-R^{13} are hydrogen, halogen or cyano,

provided that R^1 is not hydrogen, fluorine, optionally substituted lower alkyl or optionally substituted lower alkoxy, all of R^2, R^3, R^4, R^5 and R^{12} are hydrogen, or R^{13} is not hydrogen or halogen when R^6, R^7, R^8 and R^9 are all simultaneously hydrogen,

and further provided that R^1 is not methyl or acetyloxy, R^{13} is not hydrogen, optionally substituted lower alkoxycarbonyl or optionally substituted carbamoyl, or -X-Y is not methoxy when at least one of R^6, R^7, R^8 and R^9 is a substituent other than hydrogen,

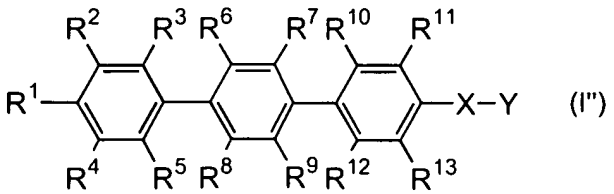
and excluding a compound of the formula (I'):



(I')

wherein $R^{1'}$ is hydrogen or hydroxy and $R^{13'}$ is hydroxy or methoxy.

40. (Twice Amended) An [immunosuppressor] immunosuppressive composition comprising a compound of the formula (I''):



(I'')

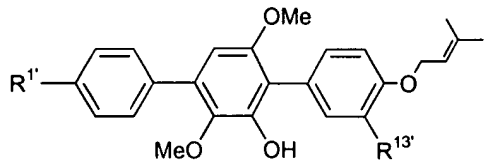
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7,R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, hydroxy, halogen, carboxy, optionally substituted lower alkyl optionally substituted, lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkenyloxy, optionally substituted lower alkylthio, optionally substituted lower alkoxycarbonyl, optionally substituted acyloxy, optionally substituted lower alkylsulfonyl, optionally substituted lower alkylsulfonyloxy, optionally substituted lower alkylsulfinyl, nitro, cyano, formyl, optionally substituted amino, optionally substituted carbamoyl, optionally substituted sulfamoyl or optionally substituted heterocyclyl,

X is -O-, $-CH_2-$, $-NR^{14}-$ wherein R^{14} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or acetyl, or -S(O)p- wherein p is an integer of 0 to 2,

Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl or optionally substituted heterocyclyl, and Y may optionally be substituted lower alkoxy when X is $-CH_2-$ and may optionally be substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyl or optionally substituted arylsulfonyl when X is -O- or $-NR^{14}-$,

R^1 and R^4, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^6 and R^7, R^8 and R^9, R^{10} and R^{11}, R^{12} and R^{13}, R^{11} and -X-Y, or R^{13} and -X-Y taken together may form a 5- or 6-membered ring which may contain one or more of O, S or NR^{15} wherein R^{15} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or optionally substituted arylsulfonyl and which may optionally be substituted,

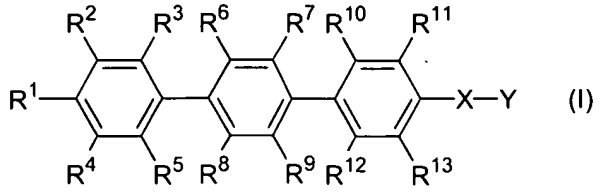
excluding a compound of the formula (I'):



(I')

wherein $R^{1'}$ is hydrogen or hydroxy and $R^{13'}$ is hydroxy or methoxy; or a pharmaceutically acceptable salt or hydrate or prodrug thereof, and a pharmaceutically acceptable excipient.

42. (Amended) A process for producing a compound of the formula (I) [of claim 34 which comprises]:



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, hydroxy, halogen, carboxy,

optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkenyloxy, optionally substituted lower alkylthio, optionally substituted lower alkoxycarbonyl, optionally substituted acyloxy, optionally substituted lower alkylsulfonyl, optionally substituted lower alkylsulfonyloxy, optionally substituted lower alkylsulfinyl, nitro, cyano, formyl, optionally substituted amino, optionally substituted carbamoyl, optionally substituted sulfamoyl or optionally substituted heterocyclyl,

X is -O-, $-CH_2-$, $-NR^{14}-$ wherein R^{14} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or acetyl, or -S(O)p- wherein p is an integer of 0 to 2,

Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl or optionally substituted heterocyclyl, and Y may optionally be substituted lower alkoxy when X is $-CH_2-$ and may optionally be substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyl or optionally substituted arylsulfonyl when X is -O- or $-NR^{14}-$,

R^1 and R^4, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^6 and R^7, R^8 and R^9, R^{10} and R^{11}, R^{12} and R^{13}, R^{11} and -X-Y, or R^{13} and -X-Y taken

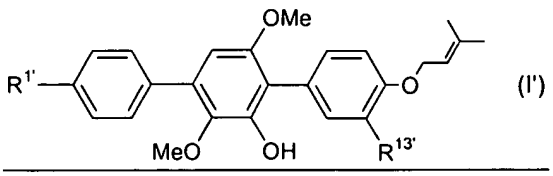
together may form a 5- or 6-membered ring which may contain one or more of O, S or NR^{15} wherein R^{15} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted arylsulfonyl and which may optionally be substituted,

excluding compounds wherein one or more of R^6, R^7, R^8 and R^9 are halogen and the others are hydrogen, compounds wherein all of R^6, R^7, R^8 and R^9 are halogen and compounds wherein all of R^2-R^{13} are hydrogen, halogen or cyano,

provided that R^1 is not hydrogen, fluorine, optionally substituted lower alkyl or optionally substituted lower alkoxy, all of R^2, R^3, R^4, R^5 and R^{12} are hydrogen, or R^{13} is not hydrogen or halogen when R^6, R^7, R^8 and R^9 are all simultaneously hydrogen,

and further provided that R^1 is not methyl or acetyloxy, R^{13} is not hydrogen, optionally substituted lower alkoxycarbonyl or optionally substituted carbamoyl, or -X-Y is not methoxy when at least one of R^6, R^7, R^8 and R^9 is a substituent other than hydrogen,

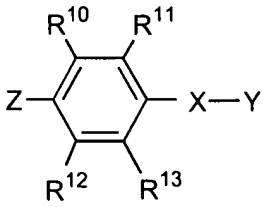
and excluding a compound of the formula (I'):



(I')

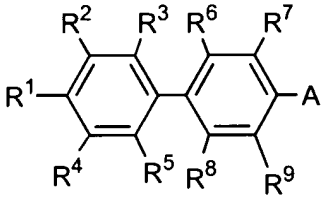
wherein $R^{1'}$ is hydrogen or hydroxy and $R^{13'}$ is hydroxy or methoxy;

said process comprising reacting a compound of the formula (II):



(II)

with a compound of the formula (III):

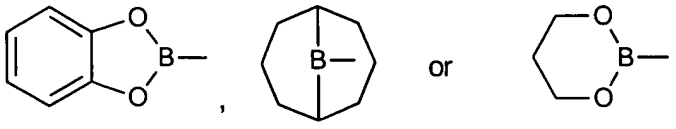


(III)

wherein, in the formulas (II) and (III), R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each described above; [independently hydrogen, hydroxy, halogen, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkenyloxy, optionally substituted lower alkylthio, optionally substituted lower alkoxycarbonyl, optionally substituted acyloxy, optionally substituted lower alkylsulfonyl, optionally substituted lower alkylsulfonyloxy, optionally substituted lower alkylsulfinyl, nitro, cyano, formyl,

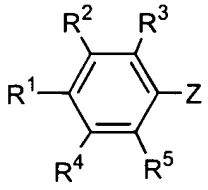
optionally substituted amino, optionally substituted carbamoyl, optionally substituted sulfamoyl or optionally substituted heterocyclyl,

X is -O-, $-CH_2-$, NR^{14}- wherein R^{14} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or acetyl, or $-S(O)_p-$ wherein p is an integer of 0 to 2, Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl or optionally substituted heterocyclyl, and Y may optionally be substituted lower alkoxy when X is $-CH_2-$ and may optionally be substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyl or optionally substituted arylsulfonyl when X is -O- or $-NR^{14}$, R^1 and R^4, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^6 and R^7, R^8 and R^9, R^{10} and R^{11}, R^{12} and R^{13}, R^{11} and -X-Y, or R^{13} and -X-Y taken together may form a 5- or 6-membered ring which may contain one or more of O, S or NR^{15} wherein R^{15} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted arylsulfonyl, and which may optionally be substituted,] either of A and Z is dihydroxyborane, di(lower)alkoxyborane, di(lower)alkylborane,



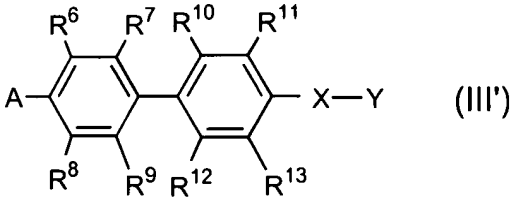
and the other is halogen or $-OSO_2(C_qF_{2q+1})-$ wherein q is an integer of 0 to 4,

or reacting a compound of the formula (II'):



(II')

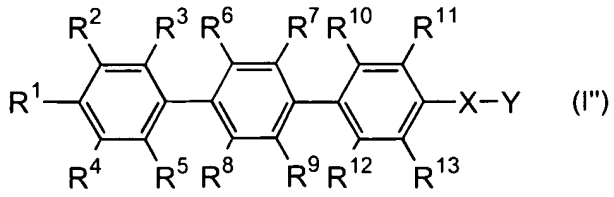
with a compound of the formula (III'):



(III')

wherein, in the formulas (II') and (III'), R^1 - R^{13}, X and Y are the same as defined above and A and Z are the same as defined in the above formulas (II) and (III).

56. (Amended) An [immunosuppressor] <u>immunosuppressive composition</u> comprising a compound of the formula (I''):



(I'')

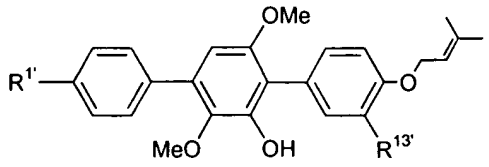
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7,R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, hydroxy, carboxy, optionally substituted lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkenyloxy, optionally substituted lower alkylthio, optionally substituted lower alkoxycarbonyl, optionally substituted acyloxy, optionally substituted lower alkylsulfonyl, optionally substituted lower alkylsulfonyloxy, optionally substituted lower alkylsulfinyl, nitro, formyl, optionally substituted amino, optionally substituted carbamoyl, optionally substituted sulfamoyl or optionally substituted heterocyclyl,

X is -O-, $-CH_2-$, $-NR^{14}-$ wherein R^{14} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or acetyl, or -S(O)p- wherein p is an integer of 0 to 2,

Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl or optionally substituted heterocyclyl, and Y may optionally be substituted lower alkoxy when X is $-CH_2-$ and may optionally be substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyl or optionally substituted arylsulfonyl when X is -O- or $-NR^{14}-$,

R^1 and R^4, R^1 and R^2, R^2 and R^3, R^4 and R^5, R^6 and R^7, R^8 and R^9, R^{10} and R^{11}, R^{12} and R^{13}, R^{11} and -X-Y, or R^{13} and -X-Y taken together may form a 5- or 6-membered ring which may contain one or more of O, S or NR^{15} wherein R^{15} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or optionally substituted arylsulfonyl and which may optionally be substituted,

excluding a compound of the formula (I'):



(I')

wherein $R^{1'}$ is hydrogen or hydroxy and $R^{13'}$ is hydroxy or methoxy; or a pharmaceutically acceptable salt or hydrate or prodrug thereof, and a pharmaceutically acceptable excipient.

Claims 57-58 have been added.